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THE COUNCIL FOR TOBACCO RESEARCH–U.S.A., INC.
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JUN 26 1975

Application for Research Grant
(Use extra pages as needed)

Date: 1975 06 23

1. Principal Investigator (give title and degrees): Stig Kullander, M.D. Professor and Chairman of Obst. and Gyn., University of Lund, Lund, Sweden

Collaborators:
Bengt Källén, M.D. Professor of Embryology
Birger Åstedt, M.D. Assoc. Prof. Obst. Gyn.
Gerhard Genser, M.D. Assoc. Prof. Obst. Gyn.

2. Institution & address:

University of Lund, Lund, Sweden

3. Department(s) where research will be done or collaboration provided:

Dpt. of Obst. Gyn, Malmö General Hospital, Malmö, Sweden
Dpt. of Embryology, University of Lund, Lund, Sweden

4. Short title of study: Influence of smoking on human foetal growth and post-natal development and on fibrinolysin in the blood of pregnant women. Accumulation and/or damage to human placental and foetal lung tissues of nicotine.

5. Proposed starting date: Jan 1. 1976.

6. Estimated time to complete: 3 years.

7. Brief description of specific research aims:
In an earlier prospective epidemiological investigation in Malmö a negative influence of smoking was shown on the weight of the children and placentae and the head circumference of the children. An increased perinatal mortality was found, due to premature placental separation with general fibrinolysin and done to increased occurrence of respiratory diseases of the new-borns. The aims of our new project are to study those findings more in detail.

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Source: https://www.industrydocuments.ucsf.edu/docs/ppdm0000

8. Brief statement of working hypothesis:

Nicotine may accumulate and/or damage enzyme systems in the placental tissue responsible for production of placental fibrinolytic inhibitors and pass through the placenta to damage the production of surfactant principles in the foetal lung tissues.

A more detailed prospective study on smoking pregnant women (Increase of biparietal head diameter measured with ultrasonic during different gestational months. Correlation to placental hormone production - HPL) and follow-up of the children, also using the mothers who stop or take-up smoking as controls during their next pregnancies would allow more firm conclusions regarding the influence of smoking as such.

9. Details of experimental design and procedures (append extra pages as necessary)

A pregnant woman is protected from bleedings by characteristic changes in the coagulation mechanism and in the fibrinolytic system. Some of the coagulation factors, protrombin, fibrinogen and factor VIII, increase during pregnancy. On the other hand there is a decrease in the fibrino-lytic activity. It is well known that the fibrinolytic activity of the blood decreases and that this activity is hardly measurable at term. Also the content of fibrinolytic activators in the vessel walls have been found to be low. This decrease of the fibrinolytic activity returns to normal levels after delivery of the placenta.

Interestingly also high amounts of the fibrinolytic inhibitors have been found to be contained in the placenta. Physiological significance of these inhibitors are presumably to prevent fatal bleedings from the placenta during pregnancy.

Smoking has been found to some extent increase fibrinolytic activity of the blood but only non-pregnant subjects have been studied so far). Hypothetically, this would increase the risk of bleedings from the placenta during pregnancy. It would therefore be of interest to investigate the influence of nicotine on the inhibitors contained in the placenta and the influence of smoking on the fibrinolytic activity of the blood during different stages of pregnancy and in the puerperium (in the same woman).

Inhibitors of the placenta were first described by Kawano et al. (Nature 217, 253, 1968) and Abildgaard and Uszinsky (Thrombosis, Diathesis Haemorrhagica 25, 580, 1971). These latter authors separated two fibrinolytic inhibitors from the human placenta. The inhibitory effect of placenta on activators released from the vessel walls has been studied in tissue culture by Åstedt et al. (Proc. Soc. Exp. Biol. Med. 139, 1421, 1972).

Our aim is to: 1) Further separate and characterize the placenta inhibitors produced in tissue culture of the placenta, further to study in tissue culture, the influence of nicotine on the production and release of the inhibitors from the placental tissue. 2) To undertake a detailed clinical study of the fibrinolytic and the inhibitory capacity of the blood in pregnant smokers compared to non-smokers.

Malmö is an ideal town for epidemiological prospective studies. 1/4 mill. of inhabitants. All deliveries are in one Dpt. of Obst. and all pregnant women are coming for prenatal routine ultrasonic screening. The population is stable and all children are followed and studied at 1 and 5 years of age in one Childrens Health Clinics.

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The detailed prospective study intended could easily be included in the routine clinical work and only some extra staffpersons must be recruited for secretarial statistical and data processing help.

We have found in Malmö in preliminary studies that nude hairless mice (without thymus) accept human foetal lung tissue. It will grow subcutaneously and its alveoli will be expanded by secretion. Injecting C_{14} nicotin to the mice - also carrying at other subcutaneous places control tissues (placenta, foetal liver and ovary) - would allow a study (liquid scintillation, EM combined with autoradiography) of accumulation and/or damage of nicotine to the human foetal lung and its production of surfactant lamellar bodies.

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10. Space and facilities available (when elsewhere than item 2 indicates, state location):

Space and facilites are available for establishing and maintaining a colony of nude mice. A tissue culture laboratory belongs to our Clinic. We have close cooperation with the Blood Coagulation Laboratory of the Hospital and an EM division at the Zoo-physiological Dpt.

11. Additional facilities required:

None.

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12. Biographical sketches of investigator(s) and other professional personnel (append):

13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available).

Included is a recent report from our Dpt. with publication lists.

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6/26/75
5.43 Swedish Kr = $1.00

14. First year budget:

A. Salaries (give names or state "to be recruited") Professional (give % time of investigator(s) even if no salary requested)	% time	Amount
		Swedish Crowns
Technical		
Secretary, to be recruited	100	50.000:-
Laboratory assistant, to be recruited (tissue culture)	100	48.000:-
Scientific assistant, to be recruited (nude mice breeding and operation)	25	13.700:-
Sub-Total for A		111.700:-
B. Consumable supplies (by major categories)		
Mice food		5.000:-
Sub-Total for B		5.000:-
C. Other expenses (itemize)		
Carrel flashs 200		3.000:-
Sephadex G 100 and columns (SR 25/100)		1.000:-
Sub-Total for C		4.000:-
Running Total of A + B + C		120.700:-
D. Permanent equipment (itemize)		
Gel-el-fores-apparatus		2.650:-
Sub-Total for D		2.650:-
E. Indirect costs (15% of A+B+C)		18.105:-
Total request		141.455:-

15. Estimated future requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Indirect Costs	Total
Year 2	117.700	5.000	4.000	0	18.105	138.805
Year 3	117.700	5.000	4.000	0	18.105	138.805

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16. Other sources of financial support: None.

List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name Stig Kullander

Signature Stig Kullander Date 19750623

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Title

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